ADAPTIVE RESYNCHRONIZATION THERAPY SYSTEM

FIELD OF THE INVENTION

The present invention relates generally to medical devices implementing a closed loop processing employing feed back control mechanism. More specifically invention deals with adaptive cardiac pacemaker and ICD devices.

BACKGROUND OF THE INVENTION

Implanted pacemakers and intracardiac cardioverter defibrillators (ICD) deliver therapy to patients suffering from various heart-diseases (Clinical Cardiac Pacing and Defibrillation –2nd edition, Ellenbogen, Kay, Wilkoff, 2000). It is known that the cardiac output depends strongly on the left heart contraction in synchrony with the right heart (see US 6,223,079). Congestive heart failures (CHF) is defined generally as the inability of the heart to deliver enough blood to meet the metabolic demand. Often CHF is caused by electrical conduction defects. The overall result is a reduced blood stroke volume from the left side of the heart. For CHF patients a permanent pacemaker with electrodes in 3 chambers, that are used to re-synchronize the left heart contraction to the right heart is an effective therapy, ("Device Therapy for Congestive Heart Failure", K. Ellenbogen et al , Elsevier Inc. (USA), 2004). The resynchronization task demands exact pacing

management of the heart chambers such that the overall stroke volume is maximized for a given heart rate (HR), where it is known that the key point is to bring the left ventricle to contract in synchrony with the right ventricle. Clearly, the re-synchronization task is patient dependent, and with each patient the best combination of pacing time intervals that restores synchrony are changed during the normal daily activities of the patient. For these reasons, next generation cardiac re-synchronization therapy devices should have online adaptive capabilities according to Hemodynamic performance.

Currently available cardiac resynchronization therapy (CRT) devices have drawbacks that prevent the achievement of an optimally delivered CRT and are listed:-

1. Programming and troubleshooting CRT device - Optimizing the CRT device using echocardiography is expansive, time consuming and operator dependent. The clinician should optimize both the atriaventricular delay (AV delay), in order to achieve maximal diastolic filling time, and the interventricular delay (VV interval) in order to achieve resynchronisation of heart chambers contractions.

2. Consistent Delivery of CRT – There are several reasons why CRT is not delivered consistently, and some times is not delivered at all for hours. Examples are failure to optimise the AV delay and low maximal tracking rate.

3. Follow Ups - The clinician must perform the complex task of optimization and programming of the CRT device, first at implantation and then at each follow-up.

4. CRT non-responders, significant number of patients do not respond to CRT after implantation.

Artificial neural networks are known to have advantages over standard algorithmic processing in performing tasks such as adaptive control and pattern recognition. Spiking neural networks architectures are a unique form of artificial neural networks that are inspired by the biological nerve system. Spiking neurons architectures, applications and learning rules are reviewed by Wolfgang Maass et. al. "Pulsed Neural Network", The MIT Press, London England (2001). Rate responsive heart stimulation device using neural networks has been proposed in US Patent 5,782,885

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic general description of an adaptive CRT system of the present invention;

FIG. 2A is a schematic major component layout of an adaptive CRT device of the invention;

Fig. 2B is a schematic major processor output connections of the processing modules of the invention;

Fig. 3 is a neural network – micro controller architecture of a device of the invention;

Fig. 4 is a state machine representation of a neuron of the learning module of the invention.

Fig. 5A is a synapse of the invention implemented as a state machine;

Fig. 5B shows a timing diagram of the dynamic synapse.

Fig. 6A is a synaptic weights adaptation rules of the present invention.

Fig. 6B is a flow chart for determining the state of a spike and the stored value at the pacing register with respect to the hemodynamic performance function of the heart;

Fig. 7 is a block diagram of an adaptive rate responsive pacemaker using right ventricular and right atrial leads as sensors and pacing the right atria.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

General System Architecture

A device of the invention is a feed – back controlled system for delivering input to the patient's body, in a manner which takes account of the body's significant physiological status relating to the delivered input.

A system of the invention is an adaptive, hemodynamic sensitive device, for regulating the heart rhythmic contraction. In **Fig. 1** to which reference is now made, a schematic description of the system of the invention shows its main building blocks. Sensors **20** feed physiological information into a learning which is typically neural network module **22** and to the algorithmic module **24**. Algorithmic module **24** receives processed data from the neural network module and supervises the adaptation of the neural network module **22**. Pulse generator **26** issues impulses at time and places as controlled only by algorithmic module **24**.

In a preferred embodiment of the invention, the system as described above forms a unitary block implanted in the patient's heart, a cardiac pacemaker or defibrillator, with sensors positioned at critical sites, and pulsing electrodes applied at strategic sites in or about the heart. In other embodiments, only the pacing module is implanted, whereas the neural network module is not implanted in the patient's body, but is communicable through a communications

link. Accordingly, the neural network module receives through a typically wireless link, information regarding hemodynamic condition of the patient and the electrical behaviour of the heart.

The main two modules in which the invention is implemented are the algorithmic module and the neural network module. In some embodiments, both modules are implemented as software modules typically in one processor, whereas in other embodiments two different processors are employed, for the algorithmic and for the neural network module, respectively.

In accordance with the present invention implementing an adaptive CRT device, a clinician programs the AV delay parameter and the VV interval parameter of the pacemaker using a programmer as with the prior art methods. The initial programmed values are used as a safety limits and a hemodynamic baseline for the present invention adaptive CRT device. The neural network module working with the deterministic algorithmic module optimises the AV delay and VV interval continuously and generates hemodynamic performance measured for example as cardiac output at all heart conditions. Whenever the neural network module fails to find a set of parameters that generates a better hemodynamic performance compared to the baseline value obtained with the initial programmed values, the adaptive CRT device switches back to pacing with the programmed fixed values.

Artificial neural networks are known to have advantages over standard algorithmic processing in performing tasks such as adaptive control and pattern recognition. However, artificial neural networks are not deterministic and may lead to quite unexpected results. In the case of cardiac pacemakers and other

life saving medical appliances, the occurrence of results beyond acceptable limits. Thus, a limit setting device, is employed in the embodiments of the present invention for confining the range of parameters provided by the neural network. Typically, artificial neural networks are designed and trained for a specific task. Unsupervised learning network architectures are very limited and are not used in many applications. Applications based on artificial neural networks that use supervised learning are far more successful then solely unsupervised autonomous networks. In accordance with the present invention, algorithmic module is used as a supervisor for the artificial neural network module. As a neural network module, the present invention preferably employs spiking neuronal networks, hereinafter referred to as SNN. Basic models of spiking neurons are reviewed by Wulfram Gerstner in Chapter 1 of "Pulsed Neural Network", edited by Wolfgang Maass and Christofer M. Bishop, The MIT Press, London England (2001). Computing methods for use with spiking neurons are presented by Wolfgang Maass in Chapter 2, of the same publication. SNN have often been implemented in VLSI which was also reflected in specific design schemes.

Adaptive cardiac resynchronisation processor elements

The adaptive CRT device aims at optimizing pacing parameters, AV delay and VV interval online, responding to the output of a hemodynamic sensor. The two parameters optimise the diastolic filling time and ensure mechanical synchronization of both ventricles. A schematic block diagram describing the pacemaker/ICD device in accordance with a preferred embodiment of the invention is shown in **Figs. 2A** and **2B**. In **Fig. 2A** implanted or external sensors

50 monitor the electrical and hemodynamic activity of the patient's heart. The monitored signals are amplified and pre – processed by an analogue circuit **52** the output of which is digitized by A/D module **54** and processed by a digital processor **56**. In the microprocessor **56** two sub - units are linked, as described schematically in **Fig. 2B**. An algorithmic module **58** performing an algorithmic process and neural network (NN) processor **60** performs a continuous adaptation process in connection with the algorithm, based on the changing circumstances detected by sensors **50**. A pulse generator of the pacemaker \ICD device **62** is driven by the processor **56**. In some embodiments of the invention processor **56** is implemented as a VLSI device.

In a preferred embodiment of the invention the NN module carries out spiking NN (SNN) processes, whereas the algorithmic module performs as a master module. In a preferred embodiment of the invention, the master processor manages the pulse generator in order to deliver pacing or shock therapy, ensuring a safe operation of the system by an algorithm with a limiting high and low thresholds, limiting rates, limiting intervals and limiting amplitudes. The NN module or slave processor's task is to generate predictions for the optimal intervals for resynchronization of the left ventricle contraction with the right ventricle contraction at all heart rates, i.e the programmable parameters AV delay and VV interval, to be described below.

The Spiking Neural Network module

In a preferred embodiment of the present invention a spiking neuron network (SNN) architecture is implemented in silicon for the following reasons:

1. SNN architectures specialize in continuous detection and classification of temporal sequences. The inputs to the SNN in the present invention are three intracardiac electrograms (IEGM) coming from the implanted electrodes in the right atria, right ventricle and outside of the left ventricle, and one or more inputs from hemodynamic sensors that are either implanted or non-invasive. All inputs described above deliver a continuous temporal signal that the SNN processors is required to process online.

2. SNN architecture has a massive parallel computation capability that allows a design of a processor with extremely low clock frequency such as 1 -10 KHz and low power consumption.

3. SNN architecture performs local computation in each neuron and synapse module and stores data locally with no need to access external, on - chip or off - chip memory modules and hence allows to scale up to a massive parallel computation power with extremely low power dissipation.

A description of a preferred embodiment using specially designed SNN processor with novel learning rules is described below with reference to **Figs 3 - 8.**

Fig. 3 shows the spiking neural network (SNN) processor architecture. The SNN processor **66** has an input layer, **70,** a middle layer, **72,** and an output neuron layer **74.** A control block, **76,** performs calculations needed for the synaptic weights adaptation rules of the SNN processor in co-operation with the micro-controller module, **78,** that are forwarded to the SNN middle and output layers. The input layer **70** receives inputs from the 3 implanted electrodes **80** from the heart chambers, data from hemodynamic sensors **82** such as impedance sensor from the right and left ventricles and pressure sensor. The three implanted

electrodes are known collectively as intra-cardiac electrograms (IEGM) which deliver also pacing signals to the heart chambers. The micro-controller can forward to the NN module processed data representing dynamic sensors such as the heart rate and a time derivative of a pressure sensor signal (dp/dt). The input layer **70** of the invention typically contains integrate and fire (I&F) neuron modules, that transform the input signals to a trains of spikes that enter the spiking neuron network of the middle layer. A description of the I&F neuron is given below. The middle layer is a network of I&F neurons containing several layers of neurons and synapses modules that connect each neuron to several neurons in an adjacent layer. All the neurons of the middle layer network are connected to the output layer.

In the output layer there are two I&F neurons, two registers and a large number of synapse modules that connect each I&F neuron to all neurons of the middle layer. One I&F neuron affects the pacing of the right ventricle the second affects the pacing of the left ventricle. The two registers store the pacing interval values to be forwarded to the micro-controller.

Fig. 4 shows an exemplary digital I&F neuron implemented as a state machine, described hereinafter. The I&F neuron is driven by excitatory and inhibitory synapses and has an internal membrane potential register (not shown). The neuron has three states, namely SUM state **84**, FIRE state **86**, and REFRACTORY state **88**. In the SUM state, the neuron sums the input excitatory post-synaptic responses (EPSR) and inhibitory post-synaptic responses (IPSR) and accumulates the result in a membrane potential register. When the membrane potential reaches a threshold value, the state-machine makes a transition to the FIRE state, generating an output spike following which, the

state-machine proceeds to the REFRACTORY state. The state machine waits for a fixed pre-defined time in the refractory state and returns to the SUM state. The synaptic module is also preferably implemented as a state machine as shown in **Fig. 5A**. The synapse has five states, namely IDLE, **90**, PRE_HEBB **92**,PSR **94**, HEBB **96**, and POST_HEBB **98**. When a spike is received from a pre-synaptic neuron, a transition to the PRE_HEBB state occurs. After a pre-defined time delay, transition to a post-synaptic response (PSR) state takes place and a PSR is emitted. The PSR is proportional to a stored synaptic weight, W, and it is a decaying function of time. After one clock period at the PSR state, the state machine enters the HEBB state. After time delay the state machine transit to a POST_HEBB state and finally it return to IDLE state.

Fig. 5B shows the three Hebb sates described above, demonstrating output neuron spikes occurrences at three different states. In the first case designated by graph **120** the output neuron spike occurs at the pre-HEBB state. In the second case designated by graph **122** the post-spike occur at the HEBB state, and in the third case designated by graph **124**, the spike occurs at the post-HEBB state. The identity of the state at which the spike has occurred is stored at the synapse every cardiac cycle and it affects the synaptic weights adaptation rules as described below.

The synaptic weights adaptation rules

The synaptic weights adaptation rules of the present invention are a combination of Hebb rule and a feedback control obtained by interaction with the environment. Hebb rule asserts that when a post-synaptic neuron fires after it

was excited by a synaptic PSR, the synapse weight is strengthened. The environment is represented by the signals of the IEGM and by a hemodynamic sensors signal. In the present invention Hebb rule is implemented as described next. Of the five states described in **Fig. 5A** to which reference is again made, three are Hebbian, namely PRE_HEBB, HEBB and POST_HEBB. In **Fig 5B** each synapse receiving an output neuron spike stores the corresponding state, i.e. PRE_HEBB, HEBB or POST_HEBB. The way these states enter the synaptic weights adaptation rules is explained below with reference to **Figs. 6A-B.**

As described above, a clinician programs the AV delay parameter and the VV interval parameter of the pacemaker as in prior art CRT devices, using accepted parameters of the art, which generates a numerical baseline representation of the sensed hemodynamic performance using the programmed parameters above. The present invention's SNN processor starts operating in normal CRT mode pacing with the programmed intervals and the two I&F neurons of the output layer learns to fire at the programmed time stored. When the I&F neurons has learned to fire at the expected time, the processor switches to adaptive CRT mode in which the AV delay and VV intervals are changed dynamically. A numerical representation of the sensed hemodynamic performance is obtained in each cardiac cycle and the synaptic weights of the SNN processor adapts accordingly to deliver the AV delay and VV intervals that results in the best hemodynamic performance. Whenever the hemodynamic performance is lower then the recorded baseline value, a switch back to the normal CRT mode pacing with the initial AV delay and VV interval values programmed by the clinician

occurs. It is expected that the SNN processor will work most of the time in the adaptive CRT mode facilitating optimal hemodynamic performance.

The synaptic weight adaptation rules applied during the normal CRT mode, takes into consideration two different occurrences. One, the deviation of the spike of the output neuron from the programmed value in terms of time. Two, the sampled Hebb states stored at each synapse as shown in **Fig. 5B** to which reference is again made. The synaptic weights adaptation rule generates a shift of the firing time of the I&F neuron in the direction of the programmed time. The synaptic weights adaptation rule are as follows:-

When the output neuron spike occurs before the programmed time, synapses that were at PRE_HEBB state increment their weights, and synapses that were at HEBB or POST_HEBB states decrement their weight. When the output spike occurs after the programmed time, synapses that were at PRE_HEBB state decrement their weight, and synapses that were at HEBB or POST_HEBB states increment their weight.

Within the adaptive CRT mode the SNN processor adapts its synaptic weights continuously interacting with the environment through the electric and hemodynamic sensors. **Fig. 6A** helps to explain the adaptive CRT mode synaptic weights adaptation rule. The output neuron fires at a time T measured from the sensed right atrial contraction every cardiac cycle, **200**. The time T is compared, at step **202**, with the time P stored at the pacing register of the output layer. If T > P the pacing register value is increased at step **204**. Else, it is decreased at step **206**. At the next cardiac cycle the pacemaker paces the heart with the updated values, stored at the pacing register. A numerical

representation of the sensed hemodynamic performance is calculated with the updated pacing values and is compared, at steps **204** and **206**, in one example the stroke volumes, SV, of the left or right ventricle is used as the hemodynamic performance criterion. Four possible states are defined by comparing the new stroke volumes with the previous stroke volumes. **Fig 6B**. shows the adaptive CRT mode learning profile for the synaptic adaptation rules. The numerical representation of the hemodynamic performance has a maximal value **220** at some pacing time interval. The task performed in the adaptive CRT mode is to modify the synaptic weight such that the value stored at the pacing register is the value that maximizes the hemodynamic performance. After a spike occurs, a corresponding state is determined as relates to the stored pacing register value stored. Spike **250** relates to the recorded pacing register **252** stored, defining a state 3. Spike **254** accordingly, as relates to pacing register **252** defines a state 1, spike **256** as relates to pacing register **258** defines state 4, spike **260** relates to pacing register **258** defining state 2. After the state associated with a spike is determined, the synaptic weight adaptation value is calculated in each synapse and its value depends on the flow diagram state and on the Hebb state stored at each synapse as was shown in **Fig. 5A** to which reference is again made. When the state associated with a spike is classified as 1 or 3 as in **Fig. 6B** to which reference is again made, the firing intervals are to be increased. When the flow diagram state is classified as 2 or 4 the firing intervals ae to be decreased. The synaptic weights are modified in each synapse separately in order to affect the firing time of the I&F neuron. Synapse in a PRE_HEBB state and is to increase its weight will cause the I&F neuron to increase firing intervals. A synapse in a

POST_HEBB state and is to increase its weight will cause the I&F neuron to decrease firing intervals.

The synaptic weights adaptation rules described above, for both the normal and the adaptive CRT modes, occur simultaneously at each output neuron, in which a different optimized function is defined for each output neuron. The hemodynamic performance is a physiological parameter such as stroke volumes of each ventricle or a processed data such as the time derivative of a pressure sensor signal.

External Adaptive CRT Device

Another preferred embodiment of the present invention is an externally adaptive CRT device for diagnostics and cardiac rehabilitation. The external adaptive CRT device receives IEGMs and hemodynamic data using a communications channel, preferably a neural network module, or other learning modules, processes the data in the external device. In this case the external adaptive CRT device is not implanted in the patient's body, and it transmits to a biventricular pacemaker or defibrillator implanted in the patient's body the optimal pacing parameters, AV delay and VV interval, to the pacemaker on-line. The diagnostics and rehabilitation procedure can be supervised by a clinician at a cardiac rehabilitation centre. The system of the invention, facilitates diagnostics and rehabilitation procedure of some form to be carried out at the patient environment (home, office etc) without the supervision of a clinician. The hemodynamic sensor used is an implanted sensor such as a pressure sensor, or a non-invasive hemodynamic sensor such as impedance sensors (such as

BioZ® sensor of CardioDynamics Inc. San Diego, California, USA) or an echocardiograph. In the case of an echocardiograph, the images of the wall motion are to be transformed to a numeric hemodynamic performance function to be used for optimisation by the present invention external adaptive CRT device.

Benefits of the adaptive CRT device

Adaptive CRT Device cardiac rehabilitation capability

The system of the present invention uses the information derived from the hemodynamic sensor in two complementary ways. One, the specific hemodynamic condition correlates with a specific hemodynamic performance representation, and two, a classification of the heart's condition is performed. For each heart condition, the optimal AV delay and VV interval are learned and updated continuously. The adaptive CRT device improves gradually the patient hemodynamic performance and hence the adaptive CRT device of the invention allows a gradual cardiac rehabilitation. This work scheme constitutes a potential clinical improvement in hemodynamic performance such as the cardiac output.

Consistent delivery of CRT

Atrial event tracking is an important issue in cardiac timing cycles in general which has also strong implication on CRT devices, as described in "Device Therapy for Congestive Heart Failure" by K. Ellenbogen et al, Elsevier Inc. (USA), 2004. In existing CRT devices, CRT is not delivered consistently due to loss of atrial tracking for hours and even for days as can be seen by pacemaker diagnostics in patients' follow-ups. Loss of atrial tracking occurs due to several reasons, for example, surpassing the programmed maximal tracking rate (MTR) during exercise. The MTR is especially important for CRT patients since when they start to exercise their cardiac output is too low for their metabolic demand, and therefore the heart rate starts increasing in order to increase cardiac output. When the patient heart rate reaches the programmed MTR (typically about 120 BPM), the implanted pacemaker stops delivery of CRT pacing and the cardiac output drops. The adaptive CRT device of the present invention, is expected to overcome the problem of loss of CRT delivery at the MTR. The classification mechanism explained above corresponding to the hemodynamic performance (maximal dp/dt for exmple), that produce the optimal AV delay and VV interval for each heart condition, potentially replaces the need to use the existing MTR limit since the optimal pacing intervals at each state are learned and stored at the spiking neuron network synapse weights. The adaptive CRT device thus produces optimal pacing parameters that obviate the need for the MTR limit.

Adaptive Rate Response

Prediction of the desired optimal rate response to the physiological demand in response to all the patient conditions is a complex task. The currently used motion sensors do not respond to physiological/mental stress or anxiety which

are not accompanied by an increase in the upper body motion. On the other hand, motion sensors respond to non-physiological events such as a bus ride, a plane take-off, operating a household drill, and other events external to the body and metabolic sensors are too slow to respond.

An adaptive rate response pacemaker in accordance with the present invention, senses the ventricle contraction and paces the right atria, with the same SNN architecture of the present invention for adaptive CRT device presented above (using only one output neuron). The SNN processor predicts the optimal timing for pacing the right atria such that the maximal dp/dt obtained with a ventrical pressure sensor is optimized in all heart conditions. In **Fig. 7** a block diagram is shown representing an adaptive rate responsive pacemaker based on the present invention. The sensors used are right atrial lead **280**, right ventricle lead **282,** and a pressure sensor, not shown. The advantage of the adaptive rate response pacemaker of the present invention is in the online, continuous adaptation to the patient hemodynamic needs with an algorithm that maximizes the hemodynamic performance as seen through a maximal dp/dt values.

Adaptive Capture Management

As discussed in US Patent 6,456,881, pacemakers with auto-capture functions preserve energy and hence have a longer battery life. They also have the advantage of causing less patient discomfort due to an excessive heart stimulation. However, compiling the auto-capture function is a complex task due

to the high variability of the heart electrical activity signals, and in particular, to the so called "fusion" phenomenon, exhibiting overlaps in time of the evoked response and internal beat. For CRT devices, capture management is even more important issue, since it is harder to capture the left ventricle comparing to the right ventricle. Usually, a higher pulse energy is used for the left ventricle and still it is not guaranteed that the left ventricle is consistently captured.

Since with the adaptive learning the pacing interval delivered to the ventricles are not constant we can predict the time difference between the evoked response in the current cardiac cycle and the evoked response of the next cardiac cycle. If the sensed event matches the prediction, it is verified as an evoked response and capture is verified. If the event is not predicted, the beat is an intrinsic one. The ability to differentiate between evoked response beat from intrinsic beat using the adaptive CRT device algorithm can be used to manage the pulse energy in order to save battery energy while ensuring capture.

Other closed loop medical devices delivering physiologically active agents can benefit from the combined system of a learning module and deterministic module that serve also as a supervisor for the learning module as presented in this invention. The architecture guarantees safe operation and at the same time allow adaptive, sensitive to the patient system. It is expected to improve performance of various closed loop, feed back controlled therapeutic medical device such as insulin pump, controlled drug delivery systems, brain stimulation devices, etc. Hence, the cardiac pacemakers and ICD devices is only one implementation of the invention.